

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Missing female patients: An observational analysis of sex ratio among outpatients in a referral tertiary care public hospital in India
AUTHORS	Kapoor, Mudit; Agrawal, Deepak; Ravi, Shamika; Roy, Ambuj; Subramanian, S V; Guleria, Randeep

VERSION 1 - REVIEW

REVIEWER	YASUHIKO MIURA JIKEI UNIV. COLLAGE OF MEDICINE, JAPAN
REVIEW RETURNED	02-Nov-2018

GENERAL COMMENTS	The reviewer completed the checklist but made no further comments.
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REVIEWER	Maria Alma Rodriguez, M.D., Professor, Lymphoma/Myeloma Department; Director of Cancer Survivorship Programs M. D. Anderson Cancer Center U.S.A.
REVIEW RETURNED	04-Dec-2018

GENERAL COMMENTS	This is a meaningful analysis using electronic health mega data to answer a question of social justice and health care resource utilization by women compared to men in a major Indian state supported hospital system. The conclusion of gender bias, with less access to health care by younger and older women, exacerbated by travel hardship related to geography, are well supported by the analysis of the data. This could be a model for analysis of unidentified or hidden biases in other systems.
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REVIEWER	Shibba Takkar Chhabra Dayanand Medical College & Hospital Unit Hero DMC Heart Institute
REVIEW RETURNED	26-Jan-2019

GENERAL COMMENTS	The manuscript is well written and aptly brings to light the issue of gender bias in seeking healthcare which is the need of the hour. It would be of interest if the authors could consider the following:
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	<p>1) The population presenting to the tertiary care hospital could be migrants working in nearby zones which could be pre dominantly males. The females less commonly migrate for work purposes hence may be present less often for health issues. This limitation may also be considered by the authors.</p> <p>2) The patients presenting to the obstetrics and gynecology department have been aptly excluded. However, it would be of interest if the numbers presenting in this department could be compared to the number of women presenting to the primary care centres in the mentioned states.</p> <p>3 Would it be feasible to know what number of patients were referred by physicians to the centre? It would be interesting if we could identify a gender bias in the referring tendency of physicians.</p>
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REVIEWER	Peter David Baade Cancer Council Queensland Australia
REVIEW RETURNED	07-Mar-2019

GENERAL COMMENTS	<p>This is an interesting study with the intent to quantify the sex inequality experienced by females attending tertiary outpatient department in Delhi, India while living in states outside Delhi. I have made specific comments below for the authors to consider. However, my main concern is that in order to answer this specific study question, the optimal study design would be to base the cohort on the residential catchment area, rather than the characteristics of the people attending one of multiple tertiary hospitals in India.</p> <p>Lines 107-110 – Given the study question, it seems counter-intuitive to select the study cohort based on hospital attendees, rather than on the geographical population of a specific geographical area.</p> <p>Line 124 – the Exclusion of Obstetrics and Gynaecology from the sampling frame should be stated in the Abstract, as should it be that these are outpatient visits only</p> <p>Lines 127-131 – Please provide further clarification about the hospital system in India. Is the AIIMS the only referral hospital in India, or are there other similar hospitals that people living in Bihar, for example, might more reasonably attend? The authors discuss this to some extent in the Discussion (lines 327-337), however I note that AIIMS is described as being only one of the premium public institutions. Are there any other “premium public institutions” that might be closer to Bihar and Uttar Pradesh?</p> <p>Line 127-131 Some clarification of the role of outpatient departments vs inpatient departments in a tertiary facility would be useful for readers not familiar with the hospital system in India.</p> <p>Line 132 – Please clarify the form/calculation of the sex ratio</p> <p>Line 147-148 – this repeats information provided in lines 144-145</p>
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	<p>Line 165 – this is an example of the confusing practice of using the terms “gender” and “sex” interchangeably throughout the manuscript. Using “sex” throughout would reduce confusion.</p> <p>Table 2 – the reporting of the model coefficients could be substantially improved. The optimal method of reporting interaction terms is to calculate and report the effects for State separately for each age group (or else by each age group separately for each State). These are calculated from the interaction model coefficients. This method of presentation would greatly simplify the textual description in the results.</p> <p>Table 2 – it would be sufficient to report the Odds Ratio and 95% confidence intervals. It would also be useful to report the overall significance of each variable (and the interaction terms) via likelihood ratio tests.</p> <p>Table 2 – can the authors report details about the departments that people visited? Was there evidence that the sex ratio differed by department? While the authors have adjusted by department, this sheds little light on how consistent the sex ratio is across the department, nor possible reasons behind the high sex ratio.</p> <p>Results section. Ideally, methods and formula should be detailed in the methods section, not the results section. Explaining the calculations in the methods section would make the results section a lot clearer.</p> <p>A statement about ethics and data custodian approval for this study is required.</p>
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REVIEWER	James Stanley University of Otago, Wellington
REVIEW RETURNED	11-Mar-2019

GENERAL COMMENTS	<p>Thank you for the opportunity to review this interesting paper.</p> <p>I have been asked to provide a statistical review of this paper, so I haven't commented on broader matters beyond methods/results (though I will add here that I think this is an important topic).</p> <p>My comments cover several related points that fit under the general concerns that (a) the methods are not always clearly described or cited, and so it is sometimes hard to tell what has been done and hence whether the analysis was appropriate; and (b) the presentation of results makes it quite hard to see “the message” in the paper. If these two issues are addressed then it will be easier to judge the results and interpretation. I have covered the major points below, and some more minor points below that. I've demarcated comments with asterisks.</p> <p>MAJOR POINTS</p> <p>Methods section: the authors do not give a definition of how they calculate sex ratio. While this is somewhat obvious from the results presentation (e.g. Table 1a), the details should be stated briefly here in the methods. At present the methods section is a little confusing as it highlights (a) the “missing female patient visits” and</p>
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(b) the regression model, but the majority of the results are based on the sex-ratio calculations. There are also several complex methods (solving interactions, predicted probabilities) that are described in the results.

Methods section (p. 5): the justification for why certain variables are adjusted for in the logistic regression is not given: for example, it seems a reasonable case can be made that “department of presentation” could be considered an adjustment variable, though that is not entirely clear. And while I understand that day of the week and month will be related to volume of presentations, there is no justification as to why these are needed for the model. A good criterion here would be whether they can act as confounders of the association in question (differences in gender of presenting patients).

Results, p. 7: the presentation of results from the logistic regression is hard to follow: e.g. lines 187-191:

“For example, 187 the odds ratio of Bihar represents that the odds of a male patient visiting the hospital from Bihar in the age group (31-44) years is approximately 1.82 (95% CI 1.74-1.91) times higher as compared to the odds of a male patient visiting from Delhi in the same age group after adjusting for the hospital department visited by the patient”

This is prone to misreading, as the phrasing “the odds of a male patient visiting the hospital...” implies that the denominator is “all people who could visit the hospital”, whereas the odds ratio is rather “the odds of a patient visiting the hospital being male...”. I think this is just a phrasing issue and hence can be fixed.

I have a bigger issue with presentation of results from Table 2 (again relatively easily fixed) which is that the presentation is not very helpful to the reader: currently the table presents the results from the logistic regression models, including interaction terms. This combination of “baseline” and interaction terms for odds ratios are notoriously hard to read/interpret, as evidenced by the fact that it takes a paragraph to explain how to read the table in the results (page 7, lines 198-208).

It would be clearer to present the stratified odds ratios for the particular combinations of groups (with their 95% CI) – that is, give the OR (male rather than female) for all combinations of State and Age group. This would only take a few more lines of results than the current presentation, and should be relatively easy to calculate (the lincom post-estimation command in Stata can do this). This stratified estimates approach should then be detailed in the methods. The text quoted above gives the estimated odds ratio for patient sex being male in Bihar age 31-44 age group. This would be somewhat akin to the predicted probabilities table in the Supplementary Results file.

Results, p. 9: The presentation of average predicted probabilities is not clear (and again should be detailed in the Methods section). The methods used to calculate this in Stata (presumably the margins command) should be given, and the exact methods stated. As it is written, it is hard to tell precisely what has been done and hence the appropriateness of this analysis.

The key approach here is probably marginal prediction: what is the expected ratio of male to female (in a given age group, for the first example) if the distribution of States is treated as fixed across age groups. This is effectively marginal standardisation: in case it is helpful (since I can't currently tell what has been done), a good reference is Muller CJ, MacLehose RF. Estimating predicted probabilities from logistic regression: different methods correspond to different target populations. *Int J Epidemiol* 2014;43(3):962-70. doi: 10.1093/ije/dyu029

Results p. 9, Table 3: I can follow the calculations and hence results here on absolute numbers of missing cases, but it's not clear why calculating the number of missing patient visits should compare each state/age group to the Delhi profile, since we already know that there are sex imbalances in visits within the Delhi region itself (this is mentioned in the Discussion, but this is a relatively major concern that should be dealt with more formally in the analysis). Following on from this point, it's not clear why the "number of missing visits for women" (p.11, lines 264-266) should only count "out of state" missed visits (ignoring Delhi): why is this number of interest?

MORE MINOR POINTS (though I think still worth clarification)

Abstract: mentions "logit model", and it would be clearer to say "logistic regression" (then this will also be consistent with the Methods section)

Results p. 5 (and elsewhere): It's very useful to have the population sex-ratio for each state reported (from the census): is it possible to incorporate this into (e.g. for Bihar the ratio was 2.36, but adjusting for population sex ratio of 1.09 gives a sex ratio of $2.36 / 1.09 = 2.17$). This is relatively minor, and may not be possible if the census results cannot be considered by age group as well.

Methods, p. 4 & 5: The calculation of "Missing female patient visits" is defined under Data sources, before the basic analysis is stated in any detail, and should ideally be placed at the end of the Statistical Analysis section.

Methods, p. 5: I don't think the regression equation is particularly helpful: the more important part here is what the model consists of (which is given in the text).

Methods, p. 5: The methods section mentions in two places (lines 144-145; lines 147-148) that clustered standard errors were used to allow for non-independence of observations from people whom visited hospital more than once. This should be condensed. Also it would be good to mention the command/option used to account for clustered standard errors in Stata, since these are a relatively complex analytical method.

Results: It would be good to report the number of unique individuals presenting to hospital in the text (currently in the Note to Table 2) along with an average number of visits per person (with any visit).

Table 2, Page 8: The column presentation isn't so helpful. It would be clearer to have one column with the odds ratio and the 95% CI in parentheses e.g. for the Bihar row: 1.82 (1.74, 1.91). Standard

	<p>error isn't helpful as the information is already used in calculating the 95% CI, plus the SE itself isn't appropriate when reporting next to an odds ratio (since the standard errors are calculated on the log scale.)</p> <p>Table 2, Page 8: The "meta-data" on sample size, adjustment variables and adjusted R-square should be removed from the table: sample size can be added to the Note for the table. On this point, adjusted R-square is not considered a great summary of a logistic regression model for various reasons: Stata is the only major statistics package that calculates this (see notes available online at https://stats.idre.ucla.edu/other/mult-pkg/faq/general/faq-what-are-pseudo-r-squareds/ if interested in details).</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1

Reviewer Name: YASUHIKO MIURA

Institution and Country: JIKEI UNIV. COLLAGE OF MEDICINE, JAPAN

Please state any competing interests or state 'None declared': NONE DECLEARED

Please leave your comments for the authors below

No Special Comments

Reviewer: 2

Reviewer Name: Maria Alma Rodriguez, M.D., Professor, Lymphoma/Myeloma Department; Director of Cancer Survivorship Programs

Institution and Country: M. D. Anderson Cancer Center, U.S.A.

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

This is a meaningful analysis using electronic health mega data to answer a question of social justice and health care resource utilization by women compared to men in a major Indian state supported hospital system. The conclusion of gender bias, with less access to health care by younger and older women, exacerbated by travel hardship related to geography, are well supported by the analysis of the data. This could be a model for analysis of unidentified or hidden biases in other systems.

Reviewer: 3

Reviewer Name: Shibba Takkar Chhabra

Institution and Country: Dayanand Medical College & Hospital Unit Hero DMC Heart Institute

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

The manuscript is well written and aptly brings to light the issue of gender bias in seeking healthcare which is the need of the hour.

It would be of interest if the authors could consider the following:

1) The population presenting to the tertiary care hospital could be migrants working in nearby zones which could be predominantly males. The females less commonly migrate for work purposes hence may be present less often for health issues. This limitation may also be considered by the authors.

Response: We thank the reviewer for the insightful review. This point is well taken but most of the migrants provide local address and thus the selection bias may not be true or work in the reverse direction.

2) The patients presenting to the obstetrics and gynecology department have been aptly excluded. However, it would be of interest if the numbers presenting in this department could be compared to the number of women presenting to the primary care centres in the mentioned states.

Response: We are unaware of data from primary care centers being available from these states to do this analysis.

3) Would it be feasible to know what number of patients were referred by physicians to the centre? It would be interesting if we could identify a gender bias in the referring tendency of physicians.

Response: We agree with your suggestion, but unfortunately this data is unavailable.

Reviewer: 4

Reviewer Name: Peter David Baade

Institution and Country: Cancer Council Queensland, Australia

Please state any competing interests or state 'None declared': None Declared

Please leave your comments for the authors below

This is an interesting study with the intent to quantify the sex inequality experienced by females attending tertiary outpatient department in Delhi, India while living in states outside Delhi. I have made specific comments below for the authors to consider. However, my main concern is that in order to answer this specific study question, the optimal study design would be to base the cohort on the residential catchment area, rather than the characteristics of the people attending one of multiple tertiary hospitals in India.

Lines 107-110 – Given the study question, it seems counter-intuitive to select the study cohort based on hospital attendees, rather than on the geographical population of a specific geographical area.

Response: We thank the reviewer for the comments. We agree that it may be best to study the patient referral from respective states. However, in the absence of that data this is a reasonable alternative to see the pattern of outpatient visits by gender from the states being studied.

Line 124 – the Exclusion of Obstetrics and Gynaecology from the sampling frame should be stated in the Abstract, as should it be that these are outpatient visits only

Response: We agree and accordingly have stated this in the abstract.

Lines 127-131 – Please provide further clarification about the hospital system in India. Is the AIIMS the only referral hospital in India, or are there other similar hospitals that people living in Bihar, for example, might more reasonably attend? The authors discuss this to some extent in the Discussion (lines 327-337), however I note that AIIMS is described as being only one of the premium public institutions. Are there any other “premium public institutions” that might be closer to Bihar and Uttar Pradesh?

Response: AIIMS, New Delhi is the largest referral tertiary care public hospital for patients from Bihar and Uttar Pradesh. We acknowledge that some patients may be attending other referral hospitals, however, we believe that this should not affect the sex ratio in outpatient visits at AIIMS, New Delhi.

Line 127-131 Some clarification of the role of outpatient departments vs inpatient departments in a tertiary facility would be useful for readers not familiar with the hospital system in India.

Response: Outpatient departments are where patients are seen in clinics for various conditions, while inpatient departments is for admitted patients.

Line 132 – Please clarify the form/calculation of the sex ratio

Response: We have made the suggested changes and defined the calculation of sex ratio in the statistical analysis.

Line 147-148 – this repeats information provided in lines 144-145

Response: We regret this oversight and have made the requisite changes.

Line 165 – this is an example of the confusing practice of using the terms “gender” and “sex” interchangeably throughout the manuscript. Using “sex” throughout would reduce confusion.

Response: In the context of discrimination we have used gender discrimination as that is the common reference to the issue on discrimination. However, in the context of quantifying gender discrimination in terms of proportion of male to female we have used sex ratios as is the common practise in the field.

Table 2 – the reporting of the model coefficients could be substantially improved. The optimal method of reporting interaction terms is to calculate and report the effects for State separately for each age group (or else by each age group separately for each State). These are calculated from the interaction model coefficients This method of presentation would greatly simplify the textual description in the results.

Response: We agree with the reviewer’s observation and have accordingly changed the presentation of Table 2.

Table 2 – it would be sufficient to report the Odds Ratio and 95% confidence intervals. It would also be useful to report the overall significance of each variable (and the interaction terms) via likelihood ratio tests.

Response: We have changed the presentation in Table 2 and report the relevant odds ratios and the 95% confidence intervals.

Table 2 – can the authors report details about the departments that people visited? Was there evidence that the sex ratio differed by department? While the authors have adjusted by department, this sheds little light on how consistent the sex ratio is across the department, nor possible reasons behind the high sex ratio.

Response: This is a good observation and we have incorporated the differences in sex ratio by the department in Figure 3.

Results section. Ideally, methods and formula should be detailed in the methods section, not the results section. Explaining the calculations in the methods section would make the results section a lot clearer.

Response: We agree with the reviewer's comment and have accordingly explained the calculations at the end of subsection on statistical analysis.

A statement about ethics and data custodian approval for this study is required.

Response: An ethics approval for data was taken from Ethics Committee, AIIMS New Delhi.

Reviewer: 5

Reviewer Name: James Stanley

Institution and Country: University of Otago, Wellington

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

Thank you for the opportunity to review this interesting paper.

I have been asked to provide a statistical review of this paper, so I haven't commented on broader matters beyond methods/results (though I will add here that I think this is an important topic).

My comments cover several related points that fit under the general concerns that (a) the methods are not always clearly described or cited, and so it is sometimes hard to tell what has been done and hence whether the analysis was appropriate; and (b) the presentation of results makes it quite hard to see “the message” in the paper. If these two issues are addressed then it will be easier to judge the results and interpretation. I have covered the major points below, and some more minor points below that. I’ve demarcated comments with asterisks.

MAJOR POINTS

Methods section: the authors do not give a definition of how they calculate sex ratio. While this is somewhat obvious from the results presentation (e.g. Table 1a), the details should be stated briefly here in the methods. At present the methods section is a little confusing as it highlights (a) the “missing female patient visits” and (b) the regression model, but the majority of the results are based on the sex-ratio calculations. There are also several complex methods (solving interactions, predicted probabilities) that are described in the results.

Response: We thank the reviewer for the comments. We have expanded the section on statistical analysis by providing clear definition on sex ratios that have been used in the analysis. We have also provided details on the methods used for computing predicted probabilities and the estimation of odds ratios involving interactions.

Methods section (p. 5): the justification for why certain variables are adjusted for in the logistic regression is not given: for example, it seems a reasonable case can be made that “department of presentation” could be considered an adjustment variable, though that is not entirely clear. And while I understand that day of the week and month will be related to volume of presentations, there is no justification as to why these are needed for the model. A good criterion here would be whether they can act as confounders of the association in question (differences in gender of presenting patients).

Response: We agree with the reviewer and cannot think of good reason why inclusion of day of the week or month would affect gender discrimination. As a result we have excluded these variables and this exclusion does not alter the main results of the paper.

Results, p. 7: the presentation of results from the logistic regression is hard to follow: e.g. lines 187-191:

“For example, 187 the odds ratio of Bihar represents that the odds of a male patient visiting the hospital from Bihar in the age group (31-44) years is approximately 1.82 (95% CI 1.74-1.91) times

higher as compared to the odds of a male patient visiting from Delhi in the same age group after adjusting for the hospital department visited by the patient”

This is prone to misreading, as the phrasing “the odds of a male patient visiting the hospital...” implies that the denominator is “all people who could visit the hospital”, whereas the odds ratio is rather “the odds of a patient visiting the hospital being male...”. I think this is just a phrasing issue and hence can be fixed.

Response: We agree with reviewer and the text has been accordingly rephrased.

I have a bigger issue with presentation of results from Table 2 (again relatively easily fixed) which is that the presentation is not very helpful to the reader: currently the table presents the results from the logistic regression models, including interaction terms. This combination of “baseline” and interaction terms for odds ratios are notoriously hard to read/interpret, as evidenced by the fact that it takes a paragraph to explain how to read the table in the results (page 7, lines 198-208).

It would be clearer to present the stratified odds ratios for the particular combinations of groups (with their 95% CI) – that is, give the OR (male rather than female) for all combinations of State and Age group. This would only take a few more lines of results than the current presentation, and should be relatively easy to calculate (the `lincom` post-estimation command in Stata can do this). This stratified estimates approach should then be detailed in the methods. The text quoted above gives the estimated odds ratio for patient sex being male in Bihar age 31-44 age group. This would be somewhat akin to the predicted probabilities table in the Supplementary Results file.

Response: We agree with the reviewer and have accordingly changed the presentation of Table 2, which now has the Odds Ratios and the 95% confidence intervals. As suggested we have used the `lincom` post estimation command in Stata with the option of to compute the odds ratios for all the combinations of State and Age group. This is also explained in detail in the section on Statistical analysis.

Results, p. 9: The presentation of average predicted probabilities is not clear (and again should be detailed in the Methods section). The methods used to calculate this in Stata (presumably the `margins` command) should be given, and the exact methods stated. As it is written, it is hard to tell precisely what has been done and hence the appropriateness of this analysis.

The key approach here is probably marginal prediction: what is the expected ratio of male to female (in a given age group, for the first example) if the distribution of States is treated as fixed across age groups. This is effectively marginal standardisation: in case it is helpful (since I can't currently tell what has been done), a good reference is Muller CJ, MacLehose RF. Estimating predicted probabilities

from logistic regression: different methods correspond to different target populations. Int J Epidemiol 2014;43(3):962-70. doi: 10.1093/ije/dyu029

Response: We agree with the reviewer and have explained in detail the marginal standardisation by using the margins I command in Stata. Detail description has been provided in the statistical analysis section.

Results p. 9, Table 3: I can follow the calculations and hence results here on absolute numbers of missing cases, but it's not clear why calculating the number of missing patient visits should compare each state/age group to the Delhi profile, since we already know that there are sex imbalances in visits within the Delhi region itself (this is mentioned in the Discussion, but this is a relatively major concern that should be dealt with more formally in the analysis). Following on from this point, it's not clear why the "number of missing visits for women" (p.11, lines 264-266) should only count "out of state" missed visits (ignoring Delhi): why is this number of interest?

Response: We agree with the reviewer that there are sex imbalances in visits within Delhi itself, hence making Delhi the reference for computation of missing female visits underestimates the total number of missing patients. As a result, we use the sex ratio of the population from the Census (2011) data for each state to compute the potential female patient visits, which is the number of female visits had they come in the same proportion of male to female as in the Census (2011) with respect to each state. Unfortunately, we do not have data from the Census (2011) on sex ratio with respect to age group in each state, so we assume that it remains the same as the overall state sex ratio across all age groups.

MORE MINOR POINTS (though I think still worth clarification)

Abstract: mentions "logit model", and it would be clearer to say "logistic regression" (then this will also be consistent with the Methods section)

Response: We agree and have edited the abstract accordingly.

Results p. 5 (and elsewhere): It's very useful to have the population sex-ratio for each state reported (from the census): is it possible to incorporate this into (e.g. for Bihar the ratio was 2.36, but adjusting for population sex ratio of 1.09 gives a sex ratio of $2.36 / 1.09 = 2.17$). This is relatively minor, and may not be possible if the census results cannot be considered by age group as well.

Response: We provide state sex ratios from the Census (2011) in Table 1b. Unfortunately, we do not have data from the Census (2011) on sex ratio with respect to age group.

Methods, p. 4 & 5: The calculation of “Missing female patient visits” is defined under Data sources, before the basic analysis is stated in any detail, and should ideally be placed at the end of the Statistical Analysis section.

Response: We agree with the reviewer and have placed the calculation at the end of the Statistical Analysis section.

Methods, p. 5: I don't think the regression equation is particularly helpful: the more important part here is what the model consists of (which is given in the text).

Response: We agree with the reviewer and have deleted the regression equation.

Methods, p. 5: The methods section mentions in two places (lines 144-145; lines 147-148) that clustered standard errors were used to allow for non-independence of observations from people whom visited hospital more than once. This should be condensed. Also it would be good to mention the command/option used to account for clustered standard errors in Stata, since these are a relatively complex analytical method.

Response: We agree with the reviewer and mentioned the Stata option `vce(cluster id)` in the Statistical Analysis section.

Results: It would be good to report the number of unique individuals presenting to hospital in the text (currently in the Note to Table 2) along with an average number of visits per person (with any visit).

Response: We agree with the reviewer and have added this in the Results section.

Table 2, Page 8: The column presentation isn't so helpful. It would be clearer to have one column with the odds ratio and the 95% CI in parentheses e.g. for the Bihar row: 1.82 (1.74, 1.91). Standard error isn't helpful as the information is already used in calculating the 95% CI, plus the SE itself isn't appropriate when reporting next to an odds ratio (since the standard errors are calculated on the log scale.)

Response: We agree with the reviewer and have edited Table 2 where we only report Odds Ratios and the 95% confidence intervals.

Table 2, Page 8: The “meta-data” on sample size, adjustment variables and adjusted R-square should be removed from the table: sample size can be added to the Note for the table. On this point, adjusted R-square is not considered a great summary of a logistic regression model for various reasons: Stata is the only major statistics package that calculates this (see notes available online at <https://stats.idre.ucla.edu/other/mult-pkg/faq/general/faq-what-are-pseudo-r-squareds/> if interested in details).

Response: We agree with the reviewer and have edited Table 2 accordingly.

VERSION 2 – REVIEW

REVIEWER	Peter Baade Cancer Council Queensland Australia
REVIEW RETURNED	08-Apr-2019

GENERAL COMMENTS	<p>1. The validity of the interpretation depends on whether, for residents of the included states, the sex ratio of referrals to other potential referral hospitals is consistent with that reported in this study. If, for example, another referral hospital had more females than males from these states, then this would substantially impact the current interpretation. This point, and/or information to rule out this possibility, should be noted in the discussion.</p> <p>2. Table 2. It would be helpful to include some indication of what the sex ratio was in the baseline category, otherwise it is difficult to interpret the OR estimates on their own. Could this be achieved by including the Sex Ratio in Table 2?</p> <p>3. I could not see the Figures in the supplied document, so am unable to comment on the validity or clarity of these.</p> <p>4. There were a number of comments in the PDF document that suggested this manuscript was still a work in progress.</p>
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REVIEWER	James Stanley Associate Professor & Biostatistician University of Otago, Wellington New Zealand
REVIEW RETURNED	09-Apr-2019

GENERAL COMMENTS	<p>Thank you for the opportunity to review the second iteration of this paper – the methods and results are substantially clearer than the first version, and it's great to see the updates. I am still focussing on the methods/results sections (including how these flow on to interpretation)</p> <p>The methods section now has a good level of detail, and it is very clear as to what analysis has been done. The presentation/layout of the results (including tables) has also substantially improved, and these changes make the results stand out much more clearly (Table 2 and the associated text in particular).</p> <p>Though some of the analyses suggested by reviewers could not be done (e.g. as they required Census data by sex and age group,</p>
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	<p>which are not available) this seems fine to me and does not affect the interpretation of the study.</p> <p>I have a few minor comments, mainly on the figures (which might need tidying up independently anyway):</p> <p>The methods section defines sex ratio calculations by age group and state, but it might be easier to first introduce the general concept (n male visits / n female visits) before going into the detailed calculations.</p> <p>Figure 1 and Figure 2: I'm not sure it's useful to have the y-axis for the figure cover the range of observed sex ratios: it might be useful to have the range extend down to 1 (as the "reference" level for sex ratio). The font is also very small and probably needs to be bigger to be legible (this may be the PDF rendering on the supplied file).</p> <p>Figure 2: the lines connecting the point estimates here aren't so appropriate, since the x-axis isn't a continuous dimension (I appreciate that the states are ordered by proximity to Delhi, but I still find the line a bit inappropriate).</p>
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VERSION 2 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 4

Reviewer Name: Peter Baade

Institution and Country: Cancer Council Queensland, Australia

Please state any competing interests or state 'None declared': None Declared

Please leave your comments for the authors below

1. The validity of the interpretation depends on whether, for residents of the included states, the sex ratio of referrals to other potential referral hospitals is consistent with that reported in this study. If, for example, another referral hospital had more females than males from these states, then this would substantially impact the current interpretation. This point, and/or information to rule out this possibility, should be noted in the discussion.

Response: We thank the reviewer for the comment and accordingly we have added the following in the discussion "Also referral to any other hospital from state and the sex ratio in them is not available and could impact sex ratios seen in this study. In the absence of data on sex ratio from other referral hospitals, we have to be cautious in interpreting our results. For example, if there are other referral hospitals visited by residents from these states, which have more female outpatient visits than male outpatient visits then this would significantly impact our current interpretation."

2. Table 2. It would be helpful to include some indication of what the sex ratio was in the baseline category, otherwise it is difficult to interpret the OR estimates on their own. Could this be achieved by including the Sex Ratio in Table 2?

Response: We have added in the note to the Table 2, "The sex ratio of outpatient visits for the reference group is 1.14."

3. I could not see the Figures in the supplied document, so am unable to comment on the validity or clarity of these.

Response: We apologize for this inconvenience.

4. There were a number of comments in the PDF document that suggested this manuscript was still a work in progress.

Response: All comments in the manuscript have been dealt with.

Reviewer: 5

Reviewer Name: James Stanley

Institution and Country: Associate Professor & Biostatistician, University of Otago, Wellington, New Zealand

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

Thank you for the opportunity to review the second iteration of this paper – the methods and results are substantially clearer than the first version, and it's great to see the updates. I am still focussing on the methods/results sections (including how these flow on to interpretation)

Response: We thank the reviewer for the comments for making the methods and results section clearer.

The methods section now has a good level of detail, and it is very clear as to what analysis has been done. The presentation/layout of the results (including tables) has also substantially improved, and these changes make the results stand out much more clearly (Table 2 and the associated text in particular).

Though some of the analyses suggested by reviewers could not be done (e.g. as they required Census data by sex and age group, which are not available) this seems fine to me and does not affect the interpretation of the study.

Response: The reviewer had made a good suggestion previously. Upon request the Census data by state and age group was made available to us, however, this came in only after we had submitted the revision on April 3rd, 2019. We have now incorporated this information in Table 1c and Table 3.

I have a few minor comments, mainly on the figures (which might need tidying up independently anyway):

The methods section defines sex ratio calculations by age group and state, but it might be easier to first introduce the general concept ($n \text{ male visits} / n \text{ female visits}$) before going into the detailed calculations.

Response: We accept the reviewers suggestions and introduced the general concept before getting into the detailed calculations.

Figure 1 and Figure 2: I'm not sure it's useful to have the y-axis for the figure cover the range of observed sex ratios: it might be useful to have the range extend down to 1 (as the "reference" level for sex ratio). The font is also very small and probably needs to be bigger to be legible (this may be the PDF rendering on the supplied file).

Response: We have modified Figure 1 and Figure 2 accordingly. We have gotten rid of the y axis, introduced a reference line at sex ratio = 1.

Figure 2: the lines connecting the point estimates here aren't so appropriate, since the x-axis isn't a continuous dimension (I appreciate that the states are ordered by proximity to Delhi, but I still find the line a bit inappropriate).

Response: We accept the reviewers comments and accordingly have modified figure 2 to a bar chart.

VERSION 3 - REVIEW

REVIEWER	James Stanley University of Otago, Wellington New Zealand
REVIEW RETURNED	03-May-2019

GENERAL COMMENTS	<p>Thank you for the updated paper. The updated census statistics are useful additions.</p> <p>With respect to Figures 1 and 2, my earlier point was that the axis was scaled inappropriately. Both figures still need a y-axis in the printed version.</p> <p>On Figure 2: a bar chart is reasonable here, but will only make sense if the origin of the y-axis is 1 (for a ratio). It's not clear what the bottom point of the y-axis is: this needs to be fixed when the y-axis is reinstated.</p>
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VERSION 3 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 5

Reviewer Name: James Stanley

Institution and Country: University of Otago, Wellington

New Zealand

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

Thank you for the updated paper. The updated census statistics are useful additions.

Response: We thank the reviewer for the suggestion.

With respect to Figures 1 and 2, my earlier point was that the axis was scaled inappropriately. Both figures still need a y-axis in the printed version.

On Figure 2: a bar chart is reasonable here, but will only make sense if the origin of the y-axis is 1 (for a ratio). It's not clear what the bottom point of the y-axis is: this needs to be fixed when the y-axis is reinstated.

Response: We thank the reviewer for the suggestions, we have reinstated the y-axis in figures 1 and 2, and the origin of the y axis is 1.00.